ASSOCIATION OF GENETIC POLYMORPHISM OF MATRIX METALLOPROTEINASE 2, 9 AND THEIR TISSUE INHIBITOR WITH SEVERITY OF PRE-ECLAMPSIA

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SRI BALAJI VIDYAPEETH
(Deemed –to-be-University)
Accredited by NAAC with 'A++' Grade
PONDICHERRY- 607402

Submitted by
SATHIYA R
REG. NO: 1805001002

Under the guidance of
Dr. SUMATHI S
Professor of Biochemistry
Mahatma Gandhi Medical College & Research Institute (MGMCRI)
Sri Balaji Vidyapeeth
(Deemed-to-be-University)

MAHATMA GANDHI MEDICAL COLLEGE AND RESEARCH INSTITUTE,
PILLAIYARKUPPAM, PONDICHERRY-607402, INDIA

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1. INTRODUCTION

Hypertensive disorder of pregnancy poses a substantial threat to both maternal and fetal health conditions. Preeclampsia (PE) is a multifaceted syndrome that complicates approximately 3–5% of all pregnancies. [1] It is depicted as a gestational condition with a hypertensive disorder diagnosed after 20 weeks of gestation and coexisting proteinuria or generalized edema, and certain forms of hematologic disorders such as thrombocytopenia or signs of end organ damage including renal impairment, abnormal liver function, pulmonary edema, and cerebral and visual disturbance. [2] The clinical presentation of PE can vary significantly, ranging from mild to severe, with severe cases leading to life-threatening complications of both the mother and the fetus.[3]

Risk factors for PE include a history of PE in previous pregnancies, chronic hypertension, preexisting diabetes, kidney disease, autoimmune disorders, obesity, advanced maternal age, multiple pregnancies, and certain genetic predispositions. Additionally, first-time pregnancies and assisted reproductive technologies are associated with a higher risk of developing PE. [4]

One of the leading causes of maternal death (and disability) worldwide is pregnancy induced hypertension. Incidence estimates from less-developed countries have varied from 4.0% to 12.3%. [5]

PE is subdivided into early-onset and late-onset groups in accordance with the gestational age. The cut-off point is usually set as gestational age(GA) 34 weeks or 37 weeks, and we can subcategorize PE into the early-onset (GA <34weeks), late-onset (GA≥34 weeks), preterm (GA<37 weeks), and term (GA ≥37 weeks). In terms of severity, PE could be classified as “nonsevere” or “severe” with the latter group exhibiting clinical features including blood pressure exceeding 160/100 mmHg, headache, visual disturbances, upper

abdominal pain, oliguria, elevated serum creatinine, thrombocytopenia (<100,000/µL), elevated level of liver enzymes, fetal growth restriction, pulmonary edema, onset at an early gestational age, and the presence of convulsion (eclampsia). [2]

According to the World Health Organization (WHO), three major complications during pregnancy—hemorrhage, hypertensive disorders of pregnancy (HDP), and infections—form a deadly triad that significantly contributes to maternal deaths and health issues worldwide. Globally, it is estimated that almost 10% of pregnancies are complicated by hypertension. [6] A prospective population-level analysis done in Mozambique, Nigeria, Pakistan and India found the prevalence of hypertension disorder as 10.9%. 10.2%, 9.3% and 10.3%, respectively. [7] A study conducted in southern India showed prevalence of various HDOP which were gestational hypertension (47.4%), PE (32.6%), chronic hypertension (8.2%) and pre-eclampsia superimposed on chronic hypertension (11.8%). [6]

A growing body of evidence suggests that genetic factors play a crucial role in determining both the susceptibility to and the severity of PE. Among the key molecular players implicated in the disease's pathogenesis are Matrix Metalloproteinases (MMPs)**,** particularly MMP-2 and MMP-9**,** and their specific inhibitors, such as Tissue Inhibitor of Metalloproteinases-1 (TIMP-1). [8] MMPs are zinc-dependent enzymes responsible for the degradation of the extracellular matrix (ECM), which is essential for normal placental development, tissue remodeling, and angiogenesis during pregnancy. Dysregulation of MMP activity has been associated with abnormal trophoblast invasion and defective spiral artery remodeling, both of which are critical processes in the development of PE. [9] Additionally, MMPs are involved in the regulation of vascular integrity and endothelial function, which are severely compromised in PE. The balance between MMPs and their inhibitors, such as TIMP-1**,** is crucial for maintaining normal placental and vascular homeostasis**.** [9]

Genetic polymorphism in MMP-2(g.–735C>T), MMP-9 (g.-1562 C/T) and TIMP-1 genes may lead to altered expression or activity of these proteins, which could disrupt the fine balance required for proper placental function, contributing to the onset and severity of PE. [10]

Several studies have explored the role of MMP-2, MMP-9, and TIMP-1 polymorphism in various cardiovascular and inflammatory diseases, but their specific association with PE remains an area of active research. Variants in these genes could influence the regulation of ECM remodeling, placental invasion, and endothelial dysfunction, all of which are key pathological features of PE.[11-14] Understanding how these genetic variants correlate with the severity of PE could provide insights into why some women develop mild forms of the disorder while others experience more severe complications, including early-onset PE.

Furthermore, the identification of specific genetic markers associated with PE could have clinical implications. These markers could serve as potential biomarker for early detection, allowing for timely intervention and better management of high-risk pregnancies. Additionally, targeting MMP and TIMP pathways may offer new therapeutic strategies to prevent or mitigate the severity of PE. Personalized medicine approaches based on genetic screening may also help tailor treatments to individual patients, improving outcomes for both mothers and infants. Therefore, this study aims to explore the association of MMP-2, MMP-9 genetic polymorphism and its tissue inhibitor (TIMP-1) with severity of PE.

2. AIM:

To study the association between single nucleotide polymorphism of matrix metalloproteinase (MMP)-2, 9 and their tissue inhibitor with severity of pre-eclampsia

2.1 OBJECTIVES:

Primary:

1. To study the circulating levels of MMP-2, MMP -9, tissue inhibitors of matrix metalloproteinase(TIMP-1) in women with pre-eclampsia and normotensive pregnant women.
2. To study the genetic polymorphism of matrix metalloproteinase MMP-2 (-735 C/T), MMP-9 (-1562 C/T) in women with pre-eclampsia and normotensive pregnant women.

Secondary:

1. To study the association between circulating levels of MMP-2, 9 and tissue inhibitors with severity of pre-eclampsia.
2. To identify the alleles associated with susceptibility to pre-eclampsia

3. REVIEW OF LITERATURE:

Huisman et al. reported that MMP-2 and MMP-9 in placental bed biopsies as early as 10–12 weeks of gestation, but their levels were not different when uncomplicated pregnancies were compared with pregnancies complicated by PE/ HELLP syndrome.[15]

Galewska et al. used distinct techniques to show that preeclamptic umbilical cord tissues (artery and vein) had lower MMP-2 and MMP-9 levels than healthy tissues. However, they found increased MMP-9 levels in plasma obtained from umbilical cord blood samples from preeclamptic newborns, and no significant differences in MMP-2, TIMP-1 and TIMP-2 compared with those measured in healthy pregnancies.[16]

Poon et al.showed that plasma MMP-9 concentrations are increased in women prior to presentation of PE. However, this biomarker did not contribute significantly to prediction of disease. [17]

Higher TIMP-1 levels were found in PE as compared with gestational hypertension (GH) and normotensive pregnant women in a study conducted by Palei et al.(2008) [10] Yet another study conducted by Palei et al. (2012) found that pregnant women with PE had significantly higher plasma MMP-2 and TIMP-2 concentrations than healthy pregnant, although the MMP2/TIMP-2 ratios were similar.[18]

Rahimi et al. showed that the presence of TT and CT alleles of (-1562C>T) polymorphism is a biomarker of susceptibility to PE in pregnant women.[19] Sahami et al reported that the frequency of CC and CT genotype was lower while the frequency of TT genotype was higher. The discrepancy may be because of different ethnicity, race, lifestyle, diet and eating habits.[20]

A study conducted in a large Tunisian Arab reported the CT genotype of MMP-9 -1562 C>T was associated with an increased risk of PE in our Tunisian cohort. However, the frequency distribution of MMP-2 -735 C>T allele and genotype polymorphism was not associated with PE.[21]

Another study conducted by Pandey et al., (2020) on preterm birth reported that in PE patients there is increased level of MMP-9 protein and increased risk of preterm was also seen in mothers bearing MMP-9 1562 TT genotype.[22]

4. SUBJECTS & METHODOLOGY:

I. Inclusion criteria:

a. Group 1: Pre-eclampsia

Pregnant women between gestational age of ≥20 – 40 weeks, new onset of hypertension with proteinuria or in the absence of proteinuria, new-onset of hypertension with the new onset of any of the following: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, cerebral or visual symptoms

b. Group 2: Healthy pregnant women who do not have present or past history of hypertensive disorders and any of the complications of pregnancy.

II. EXCLUSION CRITERIA:

Patients with known case of chronic hypertension, gestational diabetes mellitus, liver disorder, renal disorder, autoimmune disorder, endocrinological disorder and other significant medical disorder like anemia (Hb <9 mg/dL).

III. PARAMETERS STUDIED:

S. NO.	PARAMETER	METHOD
1	MMP 2	ENZYME LINKED IMMUNOSORBENT ASSAY (ELISA)
2	MMP 9	ENZYME LINKED IMMUNOSORBENT ASSAY (ELISA)
3	TIMP 1	ENZYME LINKED IMMUNOSORBENT ASSAY (ELISA)
4	HEMOGRAM	IMPEDANCE
5	TOTAL PROTEIN	BIURET METHOD
6	ALBUMIN	BROMOCRESOL GREEN METHOD
7	UREA	UREASE
8	URIC ACID	URICASE
9	CREATININE	JAFFE'S KINETICS
10	SODIUM	ION SELECTIVE ELECTRODE
11	POTASSIUM	ION SELECTIVE ELECTRODE
12	CHLORIDE	ION SELECTIVE ELECTRODE
13	ASPARTATE AMINOTRANSFERASE (AST)	KINETIC
14	ALANINE AMINOTRANSFERASE (ALT)	KINETIC
15	ALKALINE PHOSPHATASE (ALP)	KINETIC
15	LACTATE DEHYDROGENASE (LDH)	KINETIC

5. STATISTICAL ANALYSIS:

The data's were entered into MS Excel 2019 version and further analysed using SPSS (version 26.0; SPSS Inc.,Chicago IL,USA) For descriptive analysis, the categorical variables was analyzed by using frequency and percentages and the continuous variables will be analyzed by calculating mean ± Standard Deviation. For inferential analysis, the numerical data were analyzed using the "t"-test. The categorical data were analysed using Chi square test. "p" <0.05 was considered as statistically significant.

6. RESULTS:

6.1. Demographic variables between women with preeclampsia and normotensive pregnant women:

Maternal age showed significant association with PE ($p < 0.05$) whereas, Mean arterial pressure (MAP), Systolic Blood pressure (SBP), and Diastolic Blood pressure (DBP) were significantly increased in PE when compared to normotensive subjects ($p < 0.001$).

6.2. Comparison of Obstetric Outcomes among the study participants:

The study classified gestational age into two groups: pregnancies under 34 weeks and those beyond 34 weeks. Approximately 70% of participants fell into the latter category, with all findings achieving statistical significance ($p < 0.005$). Analysis of delivery mode revealed that caesarean sections were significantly more common among women with PE, while vaginal deliveries were more frequent among normotensive women ($p < 0.05$). Additionally, although most women in both groups conceived spontaneously, a significantly higher

proportion of PE women conceived via assisted reproductive methods compared to normotensive women ($p < 0.05$).

Gravida showed no statistically significant association with PE. However, parity and primiparous status showed significant differences between PE and normotensive women ($p < 0.005$).

6.3.Comparative Analysis of Complete blood cell count(CBC) Parameters in Preeclampsia and Normal Pregnancies:

The analysis of complete blood cell count results revealed that Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), and Platelet count ($p < 0.001$, $p < 0.01$, respectively), Mean Corpuscular Hemoglobin Concentration (MCHC) ($p < 0.05$) showed significance.

Receiver Operating Curve (ROC) was used to evaluate the association of these parameters with MMP levels in preeclampsia. It was determined to be AUC of 0.605, with cutoff value of 875 ng/mL for MMP-2 and 748 ng/mL for MMP-9 respectively.

6.4.Evaluation of Hepatobiliary function in preeclampsia and normotensive group:

Total protein, albumin, globulin, and the A/G ratio demonstrated highly significance between the groups ($p < 0.001$). Furthermore, the liver enzyme LDH exhibited a significant difference between the groups ($p < 0.001$) and it is highly associated with MAP($r=0.62$, $P<0.001$). Conversely, serum bilirubin, AST, ALT, and ALP levels did not show any statistically significant differences between the groups. MAP is negatively correlated with total protein and albumin in PE group ($r=P<0.001$).

6.5. Distribution of serum sodium and potassium levels in preeclampsia and normotensive pregnancies:

The analysis revealed a statistical significance in sodium ($p<0.00$) and potassium ($p<0.00$) levels between PE and normotensive pregnant women. Though the values are under reference range, the levels are notably in upper border limit which may influence the pathogenesis of PE.

6.6. Comparative analysis of kidney function in preeclampsia and normotensive pregnancy:

Significant mean differences were observed in kidney function parameters such as creatinine ($p = 0.00$) and uric acid ($p = 0.00$) between pre-eclamptic and normotensive groups, while no statistical significance was found for serum urea. Urine albumin (dipstick) categorized into trace, moderate, and high showed a positive correlation in PE group, with a chi-square value of 11.84 ($p < 0.001$).

6.7.Comparison of serum MMP levels in overall study population:

An independent t-test was used to measure the distribution of metalloproteinase levels in maternal serum samples and it shows significantly higher in the preeclampsia group compared to the normotensive group ($P < 0.001$).

6.7.1. ROC Curve Analysis of MMP-2, MMP-9, and TIMP-1: Assessing diagnostic Performance:

Increased MMP-2, 9 and TIMP-1 is associated with decrease in gestational age with AUC of 1.000, 0.999, 0.808 ***(Fig 1)***

The effect of MMP-2, MMP-9, and TIMP-1 was assessed with respect to baby weight, shows that MMP-9 has AUC of 0.775 with high sensitivity (94.1%), MMP-2 has AUC of 0.751 with sensitivity of 90.2% and TIMP-1 has AUC 0.705 with 80.4% sensitivity. ***(Fig 2)***

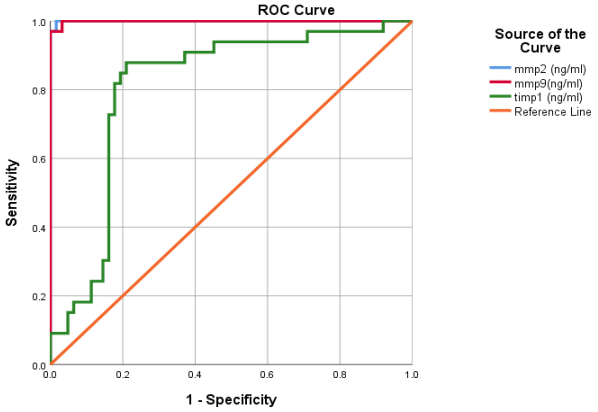

Fig 1: ROC Curve Analysis of MMP-2, MMP-9, and TIMP-1: Assessing Diagnostic Performance with reference to Gestational Age

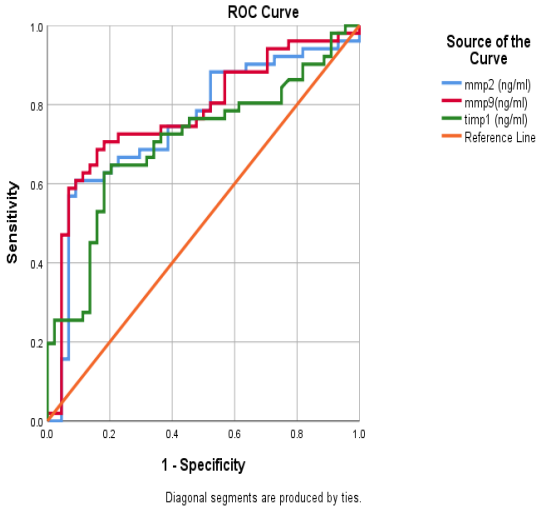

Fig 2: ROC Curve Analysis of MMP-2, MMP-9, and TIMP-1: Assessing Diagnostic Performance with reference to Baby weight

6.7.2. Correlation analysis of MMP 2, MMP 9 and TIMP 1 with biochemical parameters:

A strong positive association was found between serum MMP 9 and MMP 2 levels in PE group. ($r=0.91, p<0.001$) and there was association found between MMP 9 and TIMP 1 ($r=0.43$, $p<0.001$). The serum levels of MMP's and TIMP-1 showed positive association with mean arterial pressure in PE group. Moderate negative association was found between MMP 9 and Total protein ($r=-0.47$, $p<0.001$), albumin ($r=-0.48$, $p<0.001$).

Furthermore, there was a moderate positive correlation between MMP 9 and creatinine ($r=-0.48$, $p<0.001$), uric acid ($r=0.49$, $p<0.001$) and negative correlation with sodium ($r=-0.45$, $p<0.001$) Also it was found that MMP 9 levels were positively associated with parameters like LDH ($p<0.001$), renal profile like creatinine ($p<0.001$) and uric acid ($p<0.001$) and sodium with ($p<0.001$)

6.8.Genetic Variants:

Odds Ratios (ORs) and 95% Confidence Intervals (CI) were used to measure the likelihood of genotypes being associated with preeclampsia compared to the normotensive group.

6.8.1. Association of MMP-2(-735 C/T) gene polymorphism among study participants:

The frequency of CT genotype was significantly higher in PE group compared to the control group (OR 2.252, P < 0.005). However, no significant differences were observed in the frequencies of the wild type CC and mutant TT genotype between PE and control groups. Furthermore, the allele (C or T) difference of MMP 2 does not show any significant association between preeclampsia.

6.8.2. Association of MMP-9 (-1562 C/T) genotype in preeclampsia:

Significantly higher frequency of MMP-9 CT genotype was observed in the PE group (OR) 1.98 (95% CI: 1.09–3.59), p < 0.05). The individuals with the CC genotype are approximately (OR) 1.865 (95% CI: 1.03–3.35), p < 0.05) times more likely to have PE compared to those with the CT or TT genotypes.

6.9. Distriution of Maternal Outcomes among Study Population:

Maternal outcomes observed in the study were vision blurring, headache, edema, epigastric pain, and HELLP syndrome. All maternal complications, with the exception of HELLP syndrome, were more prevalent in the PE group (p < 0.005).

6.9.1. Association of MMP-2 (-735 C/T) gene polymorphisms with severity of preeclampsia:

The CC genotype of MMP 2 was significantly associated with a higher risk of headaches in severe PE. While maternal outcomes like vision blurring, edema and epigastric pain does not show significant associations with severity of PE

6.9.2. Association of MMP-9 (-1562 C/T) gene polymorphisms with severity of preeclampsia:

The study investigated the association of the MMP-9 genotype with maternal outcomes in severe and non-severe preeclampsia groups. The findings indicate that edema shows a significant association, with the CC genotype increasing the odds (2.354, $p = 0.042$). For vision blurring, headache, and epigastric pain, no significant associations were observed, as the p-values for these outcomes were above 0.05. This suggests that wild type (CC) genotype may play a role in the likelihood of experiencing edema but not in other measured outcomes.

6.10. Comparison of Neonatal Characteristics in overall study population:

One-way ANOVA revealed a significant difference in the rate of NICU admissions between the groups ($p < 0.005$). Preterm birth was the most common perinatal complication observed in this study. Birth weight and APGAR scores at 1 and 5 minutes showed a statistically significant association with the PE group ($p < 0.001$).

Also, it was observed that 58 neonates were delivered preterm. Of these preterm deliveries, 42 (72.4%) were between 32 to 37 weeks gestation (moderate to late preterm), 13 (22.4%) were very preterm, and 3 (5.2%) were extremely preterm. One case of neonatal death was recorded among infants born to mothers with preeclampsia (PE). Among the surviving

neonates, 28% presented with respiratory distress, and 23% showed evidence of fetal growth restriction.

6.10.1. Association of Neonatal Outcomes and MMP Gene Polymorphisms in overall study population:

Babies born between 28–32 weeks (very preterm) demonstrated a significant association in the preeclampsia group, with an odds ratio of 5.55 (95% CI: 1.47–20.86). Fetal growth retardation showed a significant positive association with the CC genotype in PE (P< 0.001) ***(Table 1).*** However, respiratory distress and preterm categories, including extremely preterm and moderate-to-late preterm groups, showed no significant association with MMP-2 and MMP-9 gene polymorphisms in the PE group.

Table 1: Association of MMP 2 & 9 genetic polymorphism with neonatal outcome in overall study population:

Neonatal outcome	Genotype	Preeclampsia		Normotensive		Odds ratio (95% CL)	p-value
		MMP 2	MMP 9	MMP 2	MMP 9		
Respiratory distress	CC	17 (63)	18 (66.7)	19 (82.6)	11 (47.8)	1.78 (0.91 – 3.50)	0.091
	CT+ TT	10 (37)	9 (32.3)	4 (17.4)	12 (52.2)		
Fetal growth retardation	CC	18 (78.3)	13 (56.5)	7 (100)	4 (57.1)	5.00 (1.97 – 12.65)	0.001*
	CT +TT	5 (21.7)	10 (43.4)	--	3 (42.9)		
PRETERM							
Extremely Preterm	CC	3 (100)	1 (33.3)	2 (100)	1 (50)	1.92 (0.30 – 12.07)	0.485
	CT +TT	--	2 (66.7)	--	1 (50)		
Very Preterm	CC	8 (61.5)	7 (53.8)	3 (100)	3 (100)	5.55 (1.47 – 20.86)	0.011*
	CT +TT	5 (38.5)	6 (46.2)	--	--		
Moderate to late	CC	28 (70)	25 (62.5)	35 (81.4)	28 (65.1)	1.19 (0.65 – 2.17)	0.565
	CT +TT	12 (30)	15 (37.5)	8 (18.6)	15 (34.9)		

*p-value <0.05 shows statistically significant

6.11. DISCUSSION:

The most important finding of our study is that women with PE have higher serum MMP-2, MMP-9 and TIMP-1 in both the groups but, there was no difference in the levels of MMP 2 and MMP 9 with respect to severity of PE. Furthermore, our results demonstrate that these three parameters were associated with gestational age and birth weight of baby. We then compared the clinical characteristics and serum biochemical parameters between the two study groups. We found that there was mild difference with regard to maternal age and BMI between the groups. In addition, PE-affected women also exhibited prominent hypertension and proteinuria, with systolic and diastolic blood pressure as well as urinary protein level much higher than the normal pregnant participants, which was consistent with their confirmed PE diagnosis.

Placental hypoxia/ischemia is believed to trigger the release of several bioactive factors including the antiangiogenic factors sFlt-1 and sEng, pro-inflammatory cytokines such as TNF-α and IL-6, HIF, ROS and AT1-AA.[23] These factors could target uteroplacental and vascular MMPs and cause further vasoconstriction of spiral arteries. Involvement of MMPs, particularly MMP-2 and MMP-9, in the pathogenesis of PE have been reported in various clinical studies. For instance, Myers et al. [24] reported that MMP-2 levels were increased in the plasma of women who later manifested PE, suggesting elevated net MMP-2 activity might contribute to PE pathophysiology. In another clinical study involving women undergoing genetic second-trimester amniocentesis, significantly elevated level of MMP-2 was detected in the amniotic fluid of women who eventually developed PE or superimposed PE, compared with normotensive women. [25]

Similarly, Palei et al. observed increased activity of MMP-9 and MMP-9/TIMP-1 ratio in pregnancies complicated by gestational hypertension, but not in those with preeclampsia

whereas MMP-2 did not show any differences with respect to healthy pregnancies and pregnancies complicated by hypertension or PE.[10] Contradictory to our results Laskowska. M et al. reported lower serum MMP 9 levels in PE group.[25] Additionally, Gerlach et al reported increased MMP 9 level could be due to additional release of this metalloproteinase by platelets and leucocytes.[26] Whereas Wang et al. [27] found that urine levels of both MMP-2 and MMP-9 were significantly higher before delivery in severe PE cases than normotensive groups.

MMP-2 and MMP-9 show strong relation to gestational age, while TIMP-1 is moderately associated with baby weight in present study. As the results are highly significant these markers could predict the outcomes of both and fetus. The frequency of MMP 2 (CT) and combined effect of CT + TT genotype was significantly higher in PE group. Our study is in line with study conducted by Rahimi et al.,[28] also reported risk of PE with CT genotype. The CC genotype of MMP 2 is significantly associated with a higher risk of headaches in severe PE additionally; MMP-9 CC genotype shows a significant association with edema with respect of severe PE. Alteration in the frequency of gene may influence the plasma levels of MMP in PE. Studied participants showed significant results with respect to edema and fetal growth retardation in wild (CC) genotype.

6.12. SUMMARY & CONCLUSION:

The study highlights the role of MMP-2 and MMP-9 gene polymorphisms and elevated metalloproteinase levels in PE. The CT genotype of MMP-9 is linked to higher PE susceptibility, while serum levels of MMP-2, MMP-9, and TIMP-1 are significantly elevated in PE patients. Maternal outcomes such as headaches and edema are associated with wild type (CC) genotype of MMP-2 and the carriage of heterozygous MMP-9 -1562 C/T genotypes, which is associated with higher MMP production. Surprisingly, fetal growth

retardation significantly associated with MMP 9 wild type (CC) genotype. These findings emphasize the genetic and biochemical contributions to PE and suggest potential biomarkers for diagnosis and risk management

6.13. LIMITATION OF THE STUDY:

- The principal limitation of the study is relatively small number of subjects.
- The assessment of the endothelial markers along with MMP at an earlier gestational age could have been more valuable.
- Lastly, potential confounding factors such as comorbidities, lifestyle, and medication use were not fully controlled, which may have influenced the results.

6.14. FUTURE SCOPE OF THE STUDY:

The primary event in preeclampsia is proposed to be poor placental perfusion which leads to widespread maternal endothelial dysfunction. However, the causes of the reduction in the placental blood flow have yet to be fully elucidated. It has been suggested that decreased placental MMP expression may cause shallow cytotrophoblastic invasion and incomplete remodelling of the spiral arteries. MMPs are also thought to act by linking placental ischemia and cardiovascular dysfunction. Follow-up studies are needed to analyse other variants in these genes and assess if altered MMP activity in PE pathogenesis.

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6.16. LIST OF PUBLICATIONS

1. **Sathiya Ramasamy**, Sumathi Saravanan, Jayanthi Rajendran, Seetesh Ghose. Clinical Sensitivity of Platelet Index and Their Association with Matrix Metalloproteinase 2 and 9: Diagnostic Approach in Preeclampsia. Foundry Journal 2024;27(10): 21-30
2. **Sathiya R**, Rajendran J, Sumathi S. COVID-19 and Preeclampsia: Overlapping Features in Pregnancy. Rambam Maimonides Med J. 2022 Jan 27;13(1):e0007. doi: 10.5041/RMMJ.10464. PMID: 35089126; PMCID: PMC8798587.
3. **Sathiya R** Diagnostic utility of Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) in Preeclampsia. Journal of Health Sciences. Conference Proceedings
4. **Sathiya Ramasamy**, Reeta Rajagambeeram, Ramesh Ramasamy, S Sumathi Assessment of Serum Electrolytes and Divalent Cation inPreeclampsia: A Comparative Study. SBV Journal of Basic, Clinical and Applied Health Science (2020): 10(3):153-57

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ORIGINAL ARTICLE

Clinical Sensitivity of Platelet Index and Their Association with Matrix Metalloproteinase 2 and 9: A Diagnostic Approach in Preeclampsia

Sathiya Ramasamy[1*], Sumathi Saravanan[2], Jayanthi Rajendran[3], Seetesh Ghose[4]

1 Department of Biochemistry, Mahatma Gandhi Medical College & Research Institute, Sri Balaji Vidyapeeth (Deemed to be University), Pondicherry, India.
2 Department of Biochemistry, Mahatma Gandhi Medical College & Research Institute, Sri Balaji Vidyapeeth (Deemed to be University), Pondicherry, India.
3 Department of Biochemistry, Mahatma Gandhi Medical College & Research Institute, Sri Balaji Vidyapeeth (Deemed to be University), Pondicherry, India.
4 Department of Obstetrics & Gynaecology, Mahatma Gandhi Medical College & Research Institute, Sri Balaji Vidyapeeth (Deemed to be University), Pondicherry, India.

***Corresponding Author: Sathiya Ramasamy**
Address: Research Scholar, Department of Biochemistry, Mahatma Gandhi Medical College & Research Institute, Sri Balaji Vidyapeeth (Deemed to be university) Puducherry, India.
sathiyar1889@gmail.com

Abstract:

Preeclampsia is a hypertensive disorder of pregnancy that remains one of the leading causes of maternal and perinatal morbidity and mortality worldwide. Matrix Metalloproteinases (MMPs), particularly MMP-2 and MMP-9, have gained attention due to their role in extracellular matrix remodeling and placental development. In this study, we aimed to establish whether alterations in platelet indices can be used alongside MMP levels as reliable early biomarkers for identifying high-risk cases. The study group consisted of women who, after 20 weeks of gestation, had blood pressure readings 140/90 mmHg on two separate occasions, at least 4 hours apart, with/without proteinuria. We analyzed clinical and laboratory data from 98 study groups with normotensives and 95 individuals with preeclampasia. Mean Corpuscular Volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) were significantly lower in the group with a p-value of 0.001 indicating possible hematological changes related to preemployment. The platelet count was also significantly reduced in the study group (p 0.001). The cut-off values for MMPs 2 and 9 were 875 and 748 ng/ml, respectively, and the area under the curve (AUC) was reported as 0.605 with 95% confidence interval (CI): 0.465-0.745 (P0.05) 0.627 with CI: 0.506-0.749 (P 0.05). The ROC curve showed a significant negative correlation between MMP 2 and Mmp 9 with platelet counts (p0.001). These findings suggest that MMP-mediated vascular damage and platelet depletion may be a potential biomarker for early detection, prognosis, and management of preeclamptic patients combined effectiveness in diagnosing and predicting the severity of the condition.

Keywords: Preeclampsia, Platelet Index, Matrix metalloproteinase (MMP)

Open Access Rambam Maimonides Medical Journal

REVIEW ARTICLE

COVID-19 and Preeclampsia: Overlapping Features in Pregnancy

Ramasamy Sathiya, M.Sc.*†, Jayanthi Rajendran, Ph.D., and Saravanan Sumathi, M.D., F.I.M.S.A.

Department of Biochemistry, Mahatma Gandhi Medical College & Research Institute, Sri Balaji Vidyapeeth (Deemed to be University), Puducherry, India

ABSTRACT

Coronavirus disease 2019 (COVID-19) is a global respiratory disease with unique features that have placed all medical professionals in an alarming situation. Preeclampsia is a hypertensive disorder of pregnancy affecting 8%–10% of India's pregnant population. Assuming that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters host cells through the angiotensin-converting enzyme 2 (ACE2) receptor, the resulting symptoms are due to vasoconstriction, caused by disturbances in the renin–angiotensin system (RAS). Other features of preeclampsia include endothelial dysfunction due to placental ischemia, leading to imbalances in angiogenic and antiangiogenic factors which result in increased blood pressure, proteinuria, altered hepatic enzymes, renal failure, and thrombocytopenia, amongst others. The increased prevalence of preeclampsia that was seen among mothers with SARS-CoV-2 infection might be due to misdiagnosis, as COVID-19 and preeclampsia have coincidental medical features. The major similarities of SARS-CoV-2-infected and preeclamptic women are a rise in pro-inflammatory cytokines, and increased serum ferritin and thrombocytopenia. Therefore, differential diagnosis might be difficult in pregnant women with COVID-19 who present with hypertension and proteinuria, thrombocytopenia, or elevated liver enzymes. The most promising markers for earlier diagnosis of preeclampsia is soluble endoglin (sEng), pregnancy-associated

Abbreviations: ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; ALT, alanine amino transferase; Ang I, angiotensin I; Ang II, angiotensin II; AST, aspartate amino transferase; BSG, basigin; COVID-19, coronavirus disease 2019; HELLP, hemolysis, elevated liver enzymes, and low platelet; IL, interleukin; INF-γ, interferon gamma; LDH, lactate dehydrogenase; PlGF, placental growth factor; RAS, renin–angiotensin system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sEng, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase-1; TMPRSS2, transmembrane protease serine 2; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

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Conflict of interest: No potential conflict of interest relevant to this article was reported.

* Ramasamy Sathiya is currently pursuing her Ph.D.

† To whom correspondence should be addressed. **E-mail:** sathiyar1889@gmail.com

Diagnostic utility of Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to Lymphocyte ratio (PLR) in preeclampsia

Sathiya R

Deptartment of Biochemistry, Mahatma Gandhi Medical College & Research Institute, Puducherry, India.

Background: Preeclampsia (PE) is new onset of hypertension after 20 weeks of gestation. NLR and PLR are now readily available inexpensive inflammatory markers that have been analysed during PE. However, many studies were analysed the diagnostic value of these ratios, but the conclusion is dissimilar due to different ethnicity. In this study, we evaluate the diagnostic value of these ratios in PE among south Indian population.

Aim & Objective: To investigate the relationship between Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) in women with preeclampsia and birth weight & neonatal APGAR score.

Materials &Methods: A case control study was conducted at a tertiary care hospital, South India. Pregnant women who were aged between 18 – 40years were recruited based on ACOG guidelines (2013). Demographic parameters maternal age, gestational age, socio-economic status, systolic and diastolic blood pressure and neonatal outcomes like birth weight, APGAR score at 1 and 5min respectively and NICU admission were collected from study subjects. About 2ml of venous blood samples were drawn from each participant to analyse parameters like Haemoglobin, Neutrophils, Lymphocytes, Platelets, NLR, and PLR. Shapiro-Wilk test was done to check data normality. Mann-Whitney test, Receiver operating curve and spearman's rank correlation was done using SPSS 16.0. A p-value of <0.05 was considered as statistically significant.

Results: Total of 60 pregnant women were recruited and they were grouped into 30 PE and 30 normotensive pregnant women. Mean age of the participants was 26.3±4.3 in control and 24.6±4.1 in PE. SBP, DBP, Neutrophils, Lymphocytes, platelets, NLR and PLR was statistically significant between the groups and haemoglobin concentration does not show significant results between the groups ($p\sim0.003$). In correlation analysis, APGAR 1min score was positively correlated and APGAR 5min score was negatively correlated with SBP, DBP, NLR, and PLR. ROC analysis of NLR shows area under curve 0.998 and PLR was 0.901 respectively. There was no significant association between birth weight and ratios.

Conclusion: In this present study, the inflammatory markers NLR and PLR were higher in women with preeclampsia and it was also associated with APGAR scores. Therefore, measuring these ratios in PE can be used as a better prognostic marker to achieve well neonatal outcome

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ORIGINAL ARTICLE

Assessment of Serum Electrolytes and Divalent Cation in Preeclampsia: A Comparative Study

Sathiya Ramasamy[1], Reeta Rajagambeeram[2], Ramesh Ramasamy[3], Sumathi Saravanan[4]

[1,2,4]Department of Biochemistry, Mahatma Gandhi Medical College and Research Institute, Puducherry, India
[3]Department of Biochemistry, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

Corresponding Author: Ramesh Ramasamy, Department of Biochemistry, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, Phone: +91 9488365657, e-mail: rameshrdr30@gmail.com

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Source of support: Sri Balaji Vidyapeeth (Deemed to be University)

Conflict of interest: None

ABSTRACT

Background and objective: Preeclampsia is one of the hypertensive disorders of pregnancy, which affects 8–10% of pregnancy and it is the leading cause of maternal and fetal morbidity and mortality. Due to the significant role of serum electrolyte and magnesium in blood pressure regulation, this study was conducted to evaluate its role in preeclampsia.

Materials and methods: A total of 30 subjects were recruited according to ACOG guidelines 2013 and 30 normotensive pregnant women, who were aged between 18 years and 40 years, who had referred from the obstetrics and gynecology department. Initially, 2 mL of blood samples were obtained from all the subjects and the samples were analyzed for serum magnesium by the calmagite method and electrolytes by the ion-selective electrode. The paired *t* test-Wilcoxon signed-rank test was performed to find if there was a significant difference between the groups. A *p* value of <0.05 was considered statistically significant.

Results: Elevated systolic, diastolic blood pressure and decreased sodium, potassium, and magnesium levels were found in preeclampsia patients compared to normotensive pregnant woman.

Conclusion: A decrease in serum magnesium and electrolyte levels contributes to the development of preeclampsia by regulating blood pressure.

MEMBERS PRESENT DURING THE MEETING

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Chair (Vector Biology),
Former Director,
ICMR-Vector Control Research Centre,
Department of Health Research,
MH & FW, Puducherry.

DEPUTY CHAIRPERSON
DR. G. SIVAGNANAM
Professor of Pharmacology,
IGMCRI, Puducherry.

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DR. LATHA CHATURVEDULA
Professor Obstetrics & Gynaecology,
JIPMER, Puducherry.

DR. R. MEDHA
Additional Professor of Biochemistry,
JIPMER, Puducherry.

DR. K. CHANDRASEGARAN
Associate Professor of Law College. (Retd),
Puducherry.

MRS. S. RAMA
Consulting Psychologist & Alternative
Medicine practitioner, Cuddalore.

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Professor of Surgery,
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MGMCRI, Puducherry.

DR. S. LOKESH
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MR. R. ANGAMOUTTOU,
Professor of social Sciences,
KGNC, Puducherry.

MEMBER SECRETARY
DR. SIVA RANGANATHAN GREEN
Associate Professor of General Medicine,
MGMCRI, Puducherry.

ADDITIONAL MEMBER SECRETARY
DR. UMA NARAYANAMURTHY
Assistant Professor of Pharmacology,
MGMCRI, Puducherry

Email: ihec@mgmcri.ac.in

CERTIFICATE OF APPROVAL

Project No: MGMCRI/IRC/02/2020/03/IHEC/141 **Date:** 28/05/2020

Project Title:

ASSOCIATION OF GENETIC POLYMORPHISM OF MATRIX METALLOPROTEINASE 2,9 AND THEIR TISSUE INHIBITORS WITH SEVERITY OF PRE-ECLAMPSIA

Study period: This approval is valid for the one year duration of the study and shall be considered for extension by IHEC, upon request with in sufficient time by the PI.

Principal Investigator: MRS. SATHIYA R

Type of review:

Full Board Review

Date of review (D/M/Y): 24th April 2020

Date of previous review, if revised application: 24TH APRIL 2019

- ✓ It is understood that the study will be conducted under your direction, in a total of ***200*** research participants, at as per the submitted protocol.
- ✓ **The IHEC approves the above mentioned study**
- ✓ For studies which will continue for more than a year, a continuing review report needs to be submitted (within1 month of the due date i.e. 11 months from the date of approval) on or before ***28/04/2021***

Member Secretary/Addl. Member Secretary

DR. UMA NARAYANAMURTHY
Member Secretary (Additional)
Institutional Human Ethics Committee
MGMCRI, Puducherry-607 402.